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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,454	09/15/2003	James D. Murray	UCAL-286	4027

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EXAMINER
HAMA, JOANNE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/663,454	MURRAY ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8,13-21 and 31-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,13-21 and 31-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the First Action on the Merits filed November 18, 2004 is acknowledged.

Claims 1, 3, 6-8, 13-16, 18, 20, and 21 are amended. Claims 31-43 are added. Claims 2 and 4 are canceled. Claims 9-12 and 22-30 are withdrawn. Applicant has correctly indicated that claims 22-30 were withdrawn from consideration in the First Office action following the Restriction Requirement.

Claims 1, 3, 5-8, 13-21, 31-43 are under consideration.

Withdrawn Rejections

35 U.S.C.§ 102(b) and 102(e)

Applicant's arguments regarding 35 U.S.C §102(b), anticipated by Miyake, et al., see pages 14-15 of Applicant's Response, filed November 18, 2004, with respect to claims 1, 2, 5, 13, 14 have been fully considered and are persuasive. The rejection of claims 1, 2, 5, 13, 14 has been withdrawn. Cholesterol 7α-hydroxylase is not a fatty acid desaturase.

Applicant's arguments regarding 35 U.S.C.§ 102(e), anticipated by Knutzon et al., see page 15 of Applicant's Response, filed November 18, 2004, with respect to claims 1, 3, 5, 13-15, 20, 21 have been fully considered and are persuasive. The rejection of claims 1, 3, 5, 13-15, 20, 21 has been withdrawn. Applicant has amended claim 1 with additional embodiments such that Knutzon et al. cannot anticipate claim 1 and its dependent claims.

35 U.S.C. § 103(a)

Applicant's arguments regarding 35 U.S.C. § 103(a), see page 16 of Applicant's Response, filed November 18, 2004, with respect to claims 1-8, 13-17, 20, 21 have been fully considered and are persuasive. The rejection of claims 1-8, 13-17, 20, 21 has been withdrawn. Applicant has amended the claim 1 with additional embodiments that Knutzon et al., in view of Ward et al. cannot anticipate claim 1 and its dependent claims.

New and Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-8, 13-21, 31-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammal whose somatic and germ cells comprise a nucleic acid sequence encoding stearoyl-CoA desaturase (SCD) operably linked to a mammary gland-specific promoter, wherein said transgene is expressed in the mammary gland of said non-human mammal and wherein milk of said non-human mammal contains said SCD transgene, a method for harvesting or processing said milk, wherein milk has higher levels of MUFA than milk obtained from a non-transgenic mammal, and a method of producing said non-human

mammal wherein SCD transgene is microinjected into a single celled non-human mammalian embyro wherein non-human mammalian embryo is transferred into a non-human mammalian female of the embryo's corresponding species, does not reasonably provide enablement for

1) any transgenic non-human mammal, comprising a transgene encoding any fatty acid desaturase, other than SCD,

2) wherein said transgene comprises a coding sequence for any fatty acid desaturase, operably linked to any animal tissue specific promoter other than mammary gland tissue promoter,

3) a method for producing said transgenic non-human animal comprising introducing any desaturase transgene into a somatic cell, forming a genetically modified somatic cell comprising a genetically modified nucleus and transferring said genetically modified somatic cell into a single-celled embyro, transferring the genetically modified embryo into a recipient female wherein the genetically modified embryo develops into a transgenic animal, and

4) a method for producing a food product comprising harvesting or processing a food product from said transgenic non-human animal, other than milk.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record stated in the First Office Action, September 2, 2004.

The claimed invention is a transgenic non-human mammal comprised of a transgene wherein the nucleic acid sequence encoding any fatty acid desaturase is operably linked to a tissue-specific promoter, and wherein the transgenic non-human mammal exhibits a decrease in saturated fatty acids in food products (e.g. milk or meat).

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Response to Arguments

Applicant's arguments filed November 18, 2004 have been fully considered but they are not persuasive.

With regards to the Applicant's arguments regarding the fact that the U.S.P.T.O has issued several patents containing claims that recite, "a transgenic non-human mammal," where such patents provide no more, and in many instances provide less, disclosure as to how to make and use the transgenic non-human mammals was being claimed (Applicant's Response, page 10, 2nd parag.), the Examiner's stance regarding this issue is that each application was assessed, based on its own merits.

As stated in the First Office Action, the specification was not enabling for the full scope of the claims. Hammer et al.'s teaching addresses another issue regarding the scope of any fatty acid desaturase gene. The art teaches that the family of fatty acid desaturases is vast. Based on the teachings of Hammer, et al., an artisan cannot predict whether any fatty acid desaturase from any species of mammal would necessarily have the same enzymatic activity it has in the original animal. With regards to the Applicant's argument that the specification provides sources for obtaining desaturase-encoding transgenes (Applicant's Response, page 11, under "Fatty acid desaturase genes"), the Examiner acknowledges that the Applicant is correct. However, based on the teachings of Hammer et al., an artisan cannot predict if any transgene can be expressed in any species of animal. An artisan would have to empirically determine if a transgene expressed in a transgenic animal has activity. For this reason, the specification is not enabling for the broad scope of any fatty acid desaturase gene. It should be pointed out that the amended claims are directed to

transgenic animals that express SCD, which is an enzyme that catalyzes stearic acid, a saturated fatty acid (no double bond containing fatty acid), to oleic acid, a monosaturated fatty acid (one double bond containing fatty acid, wherein the double bond is at the 9th carbon position). However, SCD cannot catalyze the formation of fatty acids with more than one bond (i.e. make polyunsaturated fatty acid (PUFA)) to form linoleic acid (double bonds at the 9th and 12th carbon) or α-linolenic acid (double bonds at the 9th 12th, and 15th carbon) (see Knutzon et al., Figure 1, col. 6, lines 37-44). Knutzon et al. teach that mammals cannot synthesize PUFAs (col. 3, lines 14-18) and need to obtain PUFAs from their diet. While the specification teaches the use of SCD in goats and mice, the specification does not teach the use of a desaturase that catalyzes the formation of additional double bonds in a fatty acid such that an animal could make PUFAs. The specification does demonstrate in Figure 1C that there is a higher proportion of PUFA than MUFA in transgenic goat 34. However, that does not mean that there is an increased amount of PUFA in transgenic goat milk. Rather, because this is a proportion (and no raw numbers have been taught in the specification), the results could be interpreted as the PUFA amount in goat milk is constant and the MUFA number, as reflected in Figure 1A, is dropping. That could explain the increased proportion in PUFA: MUFA content in goat 37's milk. Without guidance, the specification does not teach an artisan how to obtain transgenic animals comprised of increased levels of PUFA and MUFA in milk.

With regards to the scope of any mammalian stearly-CoA desaturase, the Examiner has performed an NCBI BLAST search on rat SCD and found that other

mammalian homologs of SCD were very similar to the rat sequence. Since the art teaches this high degree of similarity, the art enables an artisan to use any mammalian SCD in a transgenic mammal. However, with regards to the tissue in which SCD is expressed, the specification has not taught an adequate number of species of tissue specific promoters that express in an adequate number of animal species, that the enablement rejection with respect to any tissue specific promoter (see next paragraph), other than mammary gland stands.

With regards to the issue of any tissue specific promoter, the Examiner has pointed out that the specification does not teach a skilled artisan how to distinguish a transgenic mouse, wherein a mouse is comprised of a transgene operably linked to a tissue specific promoter, other than mammary gland (e.g. Example 2, intestinal epithelial cells) (First Office Action, page 7, 2nd parag.- page 8, 1st parag.). As described above, the specification and art teach how to make the transgenic mouse, but the specification does not teach how to identify a transgenic intestinal SCD mouse and how to use a mouse comprised of an intestinal epithelial promoter operably linked to a nucleic acid sequence encoding rat SCD, wherein the mouse expresses rat SCD and exhibits certain phenotypes. In addition to this, the Examiner has pointed out that promoters and enhancer elements may not function in all species of animals because they may require specific cellular factors. The specification does not provide guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient

to produce a certain phenotype (First Office Action, page 6, 2nd parag. to page 7, 1st parag.). With regards to the Applicant's argument that the specification provides sources for obtaining tissue specific promoters (Applicant's Response, page 11, under "Tissue-specific promoters"), the Examiner acknowledges that the Applicant is correct. However, because the art teaches that a promoter from one species of animal does not predictably drive expression of a gene in another species of animal, an artisan would have to empirically determine if any promoter used to express a transgene in a transgenic animal has activity. For this reason, the specification is not enabling for the broad scope of any tissue-specific promoter.

It should be made mention that the Examiner has stated that that the specification and art is enabling for the broad scope of mammary gland specific promoter (First Office Action, page 3, 1st parag.). This means that the scope is enabling for mammary gland specific promoters from any species of mammal. The reason that the scope can be broad is because the art has taught how to use mammals as bioreactors, wherein a transgene of interest is expressed in large amounts in milk (e.g. see Berg, U.S. Patent 5,667,839, patented September 16, 1997). The art teaches that unlike recombinant protein expressed in bacteria, recombinant protein produced in milk is active and soluble. It should be reiterated that while the art and specification enable an artisan to practice the claimed invention using a mammary gland specific promoter, the specification has not enabled an artisan to practice the claimed invention using any tissue specific promoter. It should be made clear at this point that while one may argue that the instant invention is a bioreactor and is thus enabling for any transgene, the art

teaches that the activity of a protein from one species of animal does not necessarily have activity when expressed in another species of animal (e.g. Hammer et al.). In the instant situation, with regards to expressing any desaturase enzyme, nothing in the specification or the art teaches that any desaturase, expressed in milk, will appropriately catalyze saturated fatty acids into unsaturated forms. Whether or not a protein has activity in another species of animal would need to be empirically determined. To determine this is undue experimentation, and thus the specification and art do not enable an artisan to practice the invention using any desaturase.

As stated in the First Office Action, the art teaches that somatic cell cloning was (and remains) unpredictable (First Office Action, page 8, 2nd parag. to page 9, 1st parag.). While the method of generating transgenic animals is well known in the art, the state of the art of cloning using somatic cells is not. The Examiner has cited Wilmut et al. (2000, Nature, 419: 538-585), who teach that "only a small proportion of embryos reconstructed using adult of fetal somatic cells developed to become live young, typically between 0 and 4%," and that "somatic cell nuclear transfer is also associated with very high rates of fetal, perinatal, and neonatal loss, and production of abnormal offspring." The Examiner also pointed to Humpherys et al. (2002, PNAS, 99:12889-12894) who teach that, "the majority of cloned mammals derived by nuclear transfer die during gestation, display neonatal phenotypes resembling large offspring syndrome, often with respiratory and metabolic abnormalities, and have enlarged and dysfunctional placentas (page 12889, parag. 1)." Due to the lack of guidance in the specification and the intractability of the art of somatic cell cloning, a skilled artisan is not enabled to

make and use a method of producing a transgenic non-human mammal comprising microinjecting a nucleus from a transgenic mammal into a somatic host cell.

For the reasons described above, the teachings of the specification and the art are not commensurate with the full scope of the claims. Because the Applicant has not provided any evidence to the contrary of what the Examiner has discussed in the First Office Action, September 2, 2004, the rejections under U.S.C. 112, first paragraph, enablement, are maintained.

Claims 1, 3, 5-8, 13-21, 31-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record stated in the First Office Action, September 2, 2004.

The claimed invention is a transgenic non-human mammal comprised of a transgene wherein the nucleic acid sequence encoding any fatty acid desaturase is operably linked to a tissue specific promoter, and wherein the transgenic non-human mammal exhibits a decrease in saturated fatty acids in food products (e.g. milk or meat).

Response to Arguments

Applicant's arguments filed November 18, 2004 have been fully considered but they are not persuasive.

With regards to any transgenic non-human mammal comprising a transgene encoding any fatty acid desaturase, the genus encompasses a large number of species that would have different structures, particular in view of the unpredictability of the art of transgenesis (First Office Action, page 13, 2nd parag. to page 14, 1st parag.). While the claims have been amended to limit the scope from "animals" to "non-human mammals," the amendment to the claims does not overcome the Examiner's rejection which pointed out that the "instant specification does not disclose the physical structure function, and, utility of a sufficient number of transgenic non-human animals that could represent the broad genus claimed (First Office Action, page 13, 2nd parag.)." The specification does not teach a representative number of mice comprised of different fatty acid desaturases, such that an artisan would have a representative number of species of transgenic mice comprising different desaturases. For this reason, any non-human mammal comprised of any fatty acid desaturase, other than SCD does not meet the criteria needed for written description.

With regards to any tissue specific promoter (First Office Action, page 14, 2nd parag, to page 15), the specification does not teach the physical structure, function, and utility of a transgenic non-human mammal comprising a nucleic acid encoding a fatty acid desaturase operably linked to any tissue specific promoter. The claimed genus encompasses any tissue specific promoter. While the specification teaches a

transgenic mouse and goat comprised of nucleic acid sequence encoding rat SCD, operably linked to a mammary tissue specific promoter, the specification does not sufficiently teach a representative number and structure of the entire genus claimed. For example, while the specification teaches a transgene comprised of a nucleic acid sequence encoding rat SCD operably lined to an epithelial tissue specific promoter, the disclosure does not teach the complete structure, function, or utility of the mouse comprising the transgene. A skilled artisan cannot envision, based on the specification the physical characteristics of said mouse, such as PUFA content, MUFA content, or epithelial cell appearance. A skilled artisan cannot envision the physical characteristics of a transgenic mouse comprising a transgene encoding SCD operably linked to any tissue specific promoter. For example, the Examiner has pointed to work by Cowan et al. who teach that transgenic pigs and mice comprised of human vascular endothelium promoters have different expression profiles from that of human. In view of the unpredictability of promoters in the art of transgenesis, the working examples in the specification does not provide teachings that overcome the unpredictability in the art, such that a skilled artisan could envision the specific structure, function, and utility of any transgenic non-human mammal comprising any fatty acid desaturase operably linked to any tissue specific promoter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5, 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 5 recite the limitation "non-human animal" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 39-43 recite the limitation "mammary gland-specific promoter" in claim 7. However, there is no gland-specific promoter in claim 7. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

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SUPERVISORY PATENT EXAMINER